REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 47-49, 54-57 and 59-66 are pending in the instant application. Claims 58 and 65 have been cancelled, and Applicants reserve the right to prosecute that subject matter, as well as the originally presented claims, in continuing applications. Claims 49, 54, 61, and 62 have been amended herein. Support for the amendments to claims 49 and 61 presented herein is found throughout the specification and in the claims as originally filed, and at least at page 15, lines 10-14. Claims 54 and 62 have been amended to exclude "fluorescently tagged" nucleic acid substrates to obviate the rejection under 35 U.S.C. §102 as discussed in detail below. Accordingly, no new matter has been added by these amendments.

I. Request for Continued Examination (RCE)

Applicants note the Examiner has acknowledged the receipt and entry of Applicants' request for continued examination (RCE) under 37 CFR §1.114, including the fee set fort in 37 CFR §1.17(e), filed on February 11, 2004. Accordingly, claims 47-49 and 54-66 are currently pending and active in the instant application.

II. Maintained Claim Rejections under 35 U.S.C. §102

Marshall

The Examiner has maintained rejection to claims 47, 49, 54-59, and 61-66 under 35 U.S.C. §102(a) as being anticipated by Marshall *et al.*, *Nature Structural Biology*, vol. 6(11): 992-94 (1999) ("Marshall"). According to the Examiner, claims 47, 59, and 66 are anticipated because Marshall discloses "aptazyme chips" in which different ribozyme ligases are immobilized on bead in wells to monitor the presence and concentrations of different metabolites or proteins (Office Action, page 2). The Examiner also asserts claims 49 and 61 are anticipated

because Marshall discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (Office Action, page 4). In addition, the Examiner asserts the following claims are anticipated: claims 54 and 62 are anticipated because Marshall discloses fluorescently tagged substrates; claims 55-56 and 63-64 are anticipated because Marshall discloses beads in wells on a multiwell plate; claim 57 is anticipated by Marshall which discloses different aptazymes immobilized in different wells; and claims 58 and 65 are anticipated by Marshall which discloses metabolites and proteins (Office Action, page 4).

Applicants traverse. Applicants submit herewith a new Affidavit by the named inventors of the instant application, Dr. Andrew D. Ellington, and Dr. Michael Robertson, Dr. J. Colin Cox, Dr. Timothy E. Reidel, and Dr. Eric A. Davidson, under 37 C.F.R. §1.131 ("the new Affidavit"). The Affidavit demonstrates that the Marshall reference is unavailable as prior art in the instant application. The Marshall reference describes the work of Dr. Ellington, a named inventor in the instant application, as well as a named author of the Marshall reference. The Marshall publication refers to work that ultimately generated the aptamer constructs, arrays, and methods of the claimed invention. In light of the fact that the Marshall reference represents the scientific publication of this work, the methods recited by pending claims 47, 49, 54-59, and 61-66 were necessarily invented before the publication date of the Marshall reference. Thus, the inventions claimed in the instant application were not known or used by others in this country, nor were the methods recited by the instant application described in a printed publication before Applicants invented them. Accordingly, Marshall is not available as prior art under 35 U.S.C. §102(a), and Applicants request that the Examiner withdraw this rejection.

Hesselberth

Claims 47, 49, 54, 58, 61-62, and 65-66 remain rejected under 35 U.S.C. §102 anticipated by Hesselberth *et al.*, *Reviews in Molecular Biotechnology*, vol. 74:15-25 (2000) ("Hesselberth"). With regard to claims 47, 59, and 66, the Examiner asserts that Hesselberth discloses methods for the "high-throughput construction of chips to sense proteomes and metabolomes" (Office Action, page 4). The Examiner also asserts that claims 49 and 61 are anticipated because Hesselberth discloses that ribozymes with appended tags can be "preferentially amplified" (Office Action, page 5). In addition, the Examiner asserts that the

following claims are anticipated: claims 54 and 62, because Hesselberth discloses fluorescent substrates; claims 58 and 65, because Hesselberth discloses proteins.

Applicants traverse. The new Affidavit submitted herewith also demonstrates that the Hesselberth reference is unavailable as prior art in the instant application. The Hesselberth reference describes the work of Dr. Ellington and Dr. Robertson, two of the named inventors in the instant application, as well as two of the named authors of the Hesselberth reference. As demonstrated in the new Affidavit, the Hesselberth reference presents work that ultimately produced the aptamer constructs, arrays, and methods claimed in the instant application. As the Hesselberth reference represents the scientific publication of this work, the methods recited by pending claims 47, 49, 54, 58, 61-62, and 65-66 were necessarily invented before the publication date of the Hesselberth reference. Thus, the inventions claimed in the instant application were not known or used by others in this country, nor were the methods recited by the instant application described in a printed publication before Applicants invented them. Accordingly, Hesselberth is not available as prior art under 35 U.S.C. §102(a), and Applicants request that the Examiner withdraw this rejection.

III. Maintained Claim Rejections under 35 U.S.C. §§102/103

Marshall

Claims 47-49 and 54-56 remain rejected under 35 U.S.C. §102(a) as being anticipated by, or in the alternative, under 35 U.S.C. §102(a) as obvious over Marshall *et al.* With regard to claims 47, 59, and 66, the Examiner asserts that Marshall discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins" (Office Action, page 7). The Examiner also asserts that while Marshall does not specifically mention the use of "automation", claims 48 and 60 are anticipated because automation would immediately be envisaged, or in the alternative, "prima facie obvious to one of ordinary skill in the art because "chips" are made for automation" (Office Action, page 8). The Examiner also asserts the following claims are anticipated: claims 49 and 61, because Marshall discloses the use of "amplification" for increasing the amount of aptamer or aptazyme with the desired characteristics; claims 54 and 62, because Marshall discloses fluorescently tagged substrates; claims 55-56 and 53-64, because Marshall discloses

beads in wells on a multiwell plate; claim 57, because Marshall discloses different aptazymes immobilized in different wells; and claims 58 and 65, because Marshall discloses metabolites (Office Action, page 8).

Applicants traverse. As described above and in the new Affidavit submitted herewith, the Marshall reference is not available as prior art under 35 U.S.C. §102 or under 35 U.S.C. §103 in the instant application. Accordingly, Applicants request that the Examiner withdraw this rejection.

Hesselberth

Claims 47-49, 56, 58-62, and 65-66 remain rejected under 35 U.S.C. §102(a) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Hesselberth *et al.* According to the Examiner, Hesselberth discloses "methods for the high-throughput construction of chips to sense proteomes and metabolomes", which anticipates claim 47. For claims 48 and 60, the Examiner asserts that "although Hesselberth does not specifically mention the use of automation with disclosed methods for using the chips, automation would be immediately envisaged, or in the alternative, prima facie obvious to one of ordinary skill in the art." The Examiner also asserts the following claims are anticipated: claims 49 and 61, because Hesselberth discloses ribozymes with appended tags can be "preferentially amplified"; claims 54 and 62, because Hesselberth discloses fluorescent substrates; claims 58 and 65, because Hesselberth discloses proteins.

Applicants traverse. As described above and in the new Affidavit submitted herewith, the Hesselberth reference is not available as prior art under 35 U.S.C. §102 or under 35 U.S.C. §103 in the instant application. Accordingly, Applicants request that the Examiner withdraw this rejection.

IV. Maintained Claim Rejections Under 35 U.S.C. §103

Marshall and Cox

Claims 47-49, 54-66 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Marshall and Cox *et al.*, *Biotechnol. Prog.*, vol. 14:845-850 (1998) ("Cox"). Claims 47, 49, 54-

59, and 61-66 have been rejected in view of the teachings of Marshall, as discussed above in the 35 U.S.C. §102(a) rejection, and it is the position of the Examiner that Marshall also renders these pending claims obvious. The Examiner has also rejected claims 48 and 60 as obvious in view of the combined teachings of Marshall and Cox. According to the Examiner, Cox teaches that *in vitro* selection can be "automated" and therefore it would have been obvious to one skilled in the art to combine the methods of Marshall with the automation processes and equipment disclosed by Cox (Office Action, page 11-12).

Applicants traverse. As described above, the Marshall reference is not available as prior art under 35 U.S.C. §102 or under 35 U.S.C. §103. Thus, the Cox reference remains the sole prior art reference. Cox, however, is insufficient to render the claimed invention obvious. The Cox reference describes methods of automated *in vitro* selection. There is no teaching or suggestion in this reference that would motivate one of ordinary skill in the art to produce aptazyme arrays for detecting an analyte and/or aptazyme reaction, let alone to automate such methods of detection. Thus, Applicants content that the methods recited by pending claims 47-49 and 54-66 remain novel and non-obvious over Cox. Accordingly, Applicants request that the Examiner withdraw this objection.

Hesselberth and Cox

Claims 47, 49, 54, 58, 61-62 and 65-66 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Hesselberth and Cox. Claims 47, 49, 54, 58, 61-62 and 65-66 stand rejected under in view of the teachings of Hesselberth as discussed in the 35 U.S.C. §102(a) rejection above. The Examiner has also rejected claims 48 and 60 as obvious in view of the combined teachings of Hesselberth and Cox. According to the Examiner, Cox teaches an *in vitro* selection that can be "automated," and therefore it would have been obvious to one of ordinary skill in the art to combine the methods of Hesselberth with the automation procedures and equipment disclosed by Cox (Office Action, page 13).

Applicants traverse. As described above and in the new Affidavit submitted herewith, the Hesselberth reference is not available as prior art under 35 U.S.C. §102(a) or under 35 U.S.C. §103(a) in the instant application. Thus, the Cox reference remains as the sole prior art reference. As described above, Cox is insufficient to render the claimed invention obvious.

Applicants content that there is no teaching or suggestion in this reference that would motivate one of ordinary skill in the art to produce the aptazyme arrays and methods recited by pending claims 47, 49, 54, 58, 61-62 and 65-66. As such, Applicants request the withdrawal of this rejection.

V. Objection to Oath/Declaration

The Examiner asserts that the Applicant's February 11, 2004 Affidavit (37 C.F.R. §1.131) is defective because inventorship is not consistent with the Affidavit. More specifically, Kristin Thompson (formerly Kristin Marshall) is not listed as a co-inventor *i.e.*, the full name of all the inventors is not provided. Accordingly, a Supplemental Declaration to the February 11, 2004 Declaration of Prior Invention under 37 C.F.R. §1.131, as well as a new Affidavit in compliance with 37 C.F.R. §1.131 are being submitted herewith.

VI. New Claim Rejections Under 35 U.S.C. §102

Breaker

The Examiner has rejected claims 47-49, 54, 58-63, and 65-66 under 35 U.S.C. §102(a) as being anticipated by Breaker et al. (WO 00/26226) ("Breaker I"). The Examiner asserts claims 47, 59 and 66 are anticipated because Breaker I discloses methods for making "aptazyme chips", more specifically, "a solid support having a heterogeneous mixture of aptazyme constructs covalently immobilized thereon" (Office Action, page 15). The Examiner also asserts the following claims are anticipated: claims 48 and 60, because Breaker I discloses automation; claims 49 and 61, because Breaker I discloses signal amplification; claims 54 and 62, because Breaker I discloses fluorescent tags; claims 55 and 63, because Breaker I discloses a multiwell plate; and claims 58 and 65, because Breaker I discloses cGMP, ATP, FMN, and cAMP, which anticipates metabolites.

Applicants traverse. Although Breaker I discloses a method for making "aptazyme chips" by covalently immobilizing aptazyme constructs to a solid support, Breaker I does not disclose how to automate a method for detecting an aptazyme reaction using immobilized aptazyme constructs, as provided by claims 47, 59, and 66 of the instant invention. The reference

to automation in Breaker I (page 21, line 19) noted by the Examiner teaches an automated method to identify DNA molecules, not an automated method for detecting aptazyme reactions, as provided by claims 48 and 60 of the instant invention. Likewise, the microtiter plate in Breaker I noted by the Examiner (page 36, line 29) teaches the use of a microtiter plate during an *in vitro* selection process, not for use in detecting an aptazyme reaction, as provided by claims 55 and 63. Additionally, Figure 16 in Breaker I discloses a biochip to which aptazyme constructs are covalently immobilized, not a multi-well plate as provided by claims 55 and 63 of the instant invention. Furthermore, the reference to signal amplification by PCR cited by the Examiner (page 10, lines 17-19) teaches signal amplification during an *in vitro* selection process, not signal amplification for detection of an aptazyme reaction using aptazyme arrays, as provided by claims 49 and 61 of the instant invention. The signal amplification for detection in the instant invention is conducted *via* PCR (see specification, page 15, "[r]ibozyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection"), not *via* enzymatic cleavage of substrate, as the Examiner asserts. To avoid vagueness in the claim language, Applicants have amended claims 49 and 61 to reflect the signal is "PCR amplified for detection".

Accordingly, Applicants have amended claims 54 and 62 to exclude fluorescently tagged nucleic acid substrates. Applicants have also canceled claims 58 and 65. Thus, due to the distinguishable differences between Breaker and the instant invention, and the corresponding claim amendments, the Applicants request the Examiner withdraw this rejection.

Asher

The Examiner has rejected claim 66 under 35 U.S.C. §102(b) as being anticipated by Asher et al. (WO 98/08974) ("Asher"). The Examiner asserts claim 66 is anticipated because Asher discloses catalytic nucleic acids and their diagnostic use. As evidence, the Examiner asserts that Example 1 and various aspects of Figure 1 in Asher disclose providing an array having one or more aptazyme constructs disposed thereon at discrete locations by immobilization of aptazyme constructs on a solid support (*e.g.*, Figure 1 steps 1, 3, and 4). In addition, the Examiner asserts that Figure 1 in Asher also discloses contacting said aptazyme constructs with a substrate tagged with a detectable label. Lastly, the Examiner asserts that Figure 1 in Asher

discloses using said aptazyme constructs to detect an analyte within a sample suspected of containing said analyte (Office Action, page 18).

Applicants traverse. The Asher reference describes a method of *in vitro* selection to identify and generate aptazyme constructs. There is no teaching or suggestion to produce aptazyme arrays from aptazyme constructs already identified through an *in vitro* selection process for detecting an analyte and/or an aptazyme reaction, let alone automate such methods of detection. In addition: (1) the aptazyme constructs used as a diagnostic tool in Asher are in suspension/solution, not immobilized to solid support or in array form, as in the instant invention; (2) Asher teaches that a solution of aptazyme constructs is added to immobilized, nucleic acid substrates, whereas in the instant invention, analytes and tagged nucleic acid substrates are added to immobilized, aptazyme constructs; and (3) the catalytic complex in Asher cleaves from the immobilized nucleic acid substrate a small detectable label, and the amount of free label is detected in the reaction medium, whereas in the instant invention, the analyte causes the tagged (labeled) nucleic acid substrate to covalently bind to the immobilized aptazyme, unbound substrate is washed away, and the immobilized labeled substrate is detected. Furthermore, Applicant's specification distinguishes the instant invention from prior inventions by stating the advantage of having covalently immobilized aptazyme constructs for *in vitro* diagnostics (see page 15, "covalent immobilization of reporters...allows stringent wash steps to be employed"). Accordingly, Applicants request that the Examiner withdraw this rejection.

VII. New Claim Rejections Under 35 U.S.C. §103

The Examiner has reminded Applicants of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants contend that each inventor was under a common obligation to assign all inventions to the University of Texas at the time of the invention dates of each claim.

The Examiner has rejected claims 47-49 and 54-66 under 35 U.S.C. §103(a) as being unpatentable over Asher and Breaker (WO 98/27104) ("Breaker II"). Claims 47, 49, 54-55, 58-59, 61-63, and 65-66 have been rejected in view of the teachings of Asher as discussed above. The Examiner has also rejected claims 47-48, 56-58, 60, and 65, in view of the combined

teachings of Asher and Breaker II. According to the Examiner, Breaker II teaches the use of covalent bonding of aptazymes to a solid support, and therefore it would have been obvious to one skilled in the art at the time the invention was made to make the immobilized array of aptazymes as taught by Asher with covalent attachment of aptazymes to the solid support as taught by Breaker II, instead of by Streptavidin/Avidin immobilization as taught by Asher (Office Action, page 22).

Applicants traverse. As discussed above, Asher is distinguishable from the instant invention because Asher teaches a method for identifying aptazyme constructs through a method of *in vitro* selection, and using aptazymes in solution/suspension as a diagnostic tool, not in an immobilized array form, as in the instant invention. The Examiner asserts that Breaker II teaches automation (Breaker II line 17, page 21). Applicants traverse. The use of automation in Breaker II refers to an automated *in vitro* selection method for selecting DNA molecules, not an automated method for detecting aptazyme reactions using aptazyme arrays. Thus, Breaker II is insufficient to render the claimed invention obvious because there is no teaching or suggestion in this reference that would motivate one of ordinary skill in the art to produce an automated method for detecting aptazyme reactions using aptazyme arrays, as recited by pending claims 47-47 and 54-66. Accordingly, Applicants request that the Examiner withdraw this rejection.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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